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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

RESPONSE UNDER RULE 116
EXPEDITED HANDLING PROCEDURES

In re Patent Application of Atty Dkt. 249-118
C# M#

YOKOI et al TC/A.U. 1647

Serial No. 09/680,514 Examiner: Spector

Filed: October 6, 2000 Date: March 12, 2004

Title: HG-CSF FUSION POLYPEPTIDE HAVING C-MPL ACTIVITY, DNA CODING FOR SAME AND METHODS OF TREATING ANEMIA USING SAME

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

RESPONSE/AMENDMENT/LETTER

This is a response/amendment/letter in the above-identified application and includes an attachment which is hereby incorporated by reference and the signature below serves as the signature to the attachment in the absence of any other signature thereon.

☐ **Correspondence Address Indication Form Attached.**

Fees are attached as calculated below:

Total effective claims after amendment **0** minus highest number previously paid for **20** (at least 20) = 0 x $ 18.00	$	0.00
Independent claims after amendment **0** minus highest number previously paid for **3** (at least 3) = 0 x $ 86.00	$	0.00
If proper multiple dependent claims now added for first time, add $290.00 (ignore improper)	$	0.00
Petition is hereby made to extend the current due date so as to cover the filing date of this paper and attachment(s) ($110.00/1 month; $420.00/2 months; $950.00/3 months)	$	110.00
Terminal disclaimer enclosed, add $ 110.00	$	0.00
☐ First/second submission after Final Rejection pursuant to 37 CFR 1.129(a) ($770.00) ☐ Please enter the previously unentered , filed ☐ Submission attached	$	0.00
Subtotal	$	**110.00**
If "small entity," then enter half (1/2) of subtotal and subtract ☐ Applicant claims "small entity" status. ☐ Statement filed herewith	-$	0.00
Rule 56 Information Disclosure Statement Filing Fee ($180.00)	$	0.00
Assignment Recording Fee ($40.00) 03/15/2004 SDENBOB1 00000069 09680514	$	0.00
Other: 01 FC:1251 110.00 OP		**0.00**
TOTAL FEE ENCLOSED	$	**110.00**

The Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Account No. 14-1140. A duplicate copy of this sheet is attached.

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By Atty: B. J. Sadoff, Reg. No. 36,663

Signature: B J Sadoff

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

YOKOI et al | Atty. Ref.: 249-118; Confirmation No. 9035

Appl. No. 09/680,514 | Group: 1647

Filed: October 6, 2000 | Examiner: Spector

For: HG-CSF FUSION POLYPEPTIDE HAVING C-MPL ACTIVITY, DNA CODING FOR SAME AND METHODS OF TREATING ANEMIA USING SAME

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March 12, 2004

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

RESPONSE UNDER RULE 116

Responsive to the Official Action dated June 12, 2003, entry and consideration of the following remarks are requested; the period for response having been extended up to and including March 12, 2004, by submission of the extension petition, petition fee, Notice of Appeal and Notice of Appeal fee, filed December 12, 2003 and the attached one month extension petition and one month extension fee.

Claims 10-18 are pending. Claims 16-18 have been withdrawn from consideration. Claims 10-15 are under active consideration.

Acknowledgment of the applicants claim for domestic priority to application Serial No. 08/765,337, is requested in the Examiner's next Action.

Acceptance of the drawings, or specific objection to the same, is requested in the Examiner's next Action.

Reconsideration and withdrawal of the "new matter" rejection stated on page 2 of the Office Action dated June 12, 2003, is requested. The incorporation by reference to the parent application was submitted with the originally-filed application on October 6, 2000, on the applicants Request for filing in the originally-filed application as a continuation-in-part of Serial No. 08/765,337. Unfortunately, the Amendment of October 6, 2000, incorrectly identified the series number of the prior application however the same was corrected in the Amendment of December 23, 2002, in specific response to the Examiner's helpful comment on page 3 of the Office Action dated June 21, 2002. The Amendment correcting the first paragraph of the application inserted with the originally-filed application on October 6, 2000, is not believed to introduce new matter and reconsideration and withdrawal of the new matter objection stated on page 2 of the Paper No. 12 is requested.

More specifically, the Request for Filing Application Under Rule 1.53(b) filed October 6, 2000, with the application, includes the following request:

"Please amend the specification by inserting before the first line --This is a continuation-in-part of application Serial No. 09/765,337, filed December 23, 1996, now pending, the entire content of which is hereby incorporated by reference in this application.--" As noted above, the Series number was inadvertently included in this paragraph and was subsequently corrected.

The Request, filed with the application on October 6, 2000, is believed to have explicitly incorporated-by-reference the entire text of Application Serial No. 08/765,337, with the effect that whole text of Application Serial No. 08/765,337, was, in legal effect, a part of the papers filed with the Patent Office on October 6, 2000.

Incorporation-by-reference of text and essential material is a well accepted practice in U.S. Patent Law.

Specifically, the court in In re de Seversky, 177 USPQ 144 (CCPA 1973) (copy attached as Exhibit 1), held, relying on In re Lund, 153 USPQ 625 (1967) (copy attached as Exhibit 2), that merely identifying a subsequent application as a "continuation-in-part" of an earlier application was insufficient to explicitly incorporate by reference the full text of the earlier application, or an aspect thereof, in to the later application.

The de Seversky court explained as follows:

> To be sure, the statement that an application is a continuation-in-part, or a continuation, or a division, or in part a continuation of another application is in a broad sense a "reference" to the earlier application, but a mere reference to another application, or patent, or publication is not an incorporation of anything therein into the application containing such reference for the purposes of the disclosure required by 35 U.S.C. 112. Likewise it does not serve to bring a disclosure within the requirements of 35 U.S.C. 120 so as to give a later application the benefit of the filing date of an earlier application. The later application must itself contain the necessary disclosure. As we said in Lund, 153 USPQ at 631,
>
> **'As the expression itself implies, the purpose of "incorporation by reference" is to make one document become a part of another document by referring to the former in the latter *in such a manner* that it is apparent that the cited document is part of the referencing document as if it were fully set out therein.** [[italicized] Emphasis added [in original; bold underlined emphasis added herein] .]'

Again, the undersigned notes that the papers filed October 6, 2000, contain the following statement:

> "Please amend the specification by inserting before the first line --This is a continuation-in-part of application Serial No. 09/765,337, filed December 23, 1996, now pending, the entire content of which is hereby incorporated by reference in this application.--"

The above-quoted statement was clearly made "in such a manner that it is apparent that the cited document is part of the referencing document as if it were fully set out therein", as described by the in the court in In re Lund and In re de Seversky.

Moreover, the Solicitor has considered in In re Yang and Olsen, 177 USPQ 88 (Patent Office Solicitor 1973) (copy attached as Exhibit 3) the legal definition and consequences of an incorporation-by-reference. Specifically, the Solicitor in Yang considered whether an incorporation-by-reference in a later application, which issued as a patent, should make the incorporated application available to the public. The Solicitor in Yang found that the patent states that the application is "hereby incorporated by reference" (column 1, lines 31-36). The Solicitor in Yang relied on the following definition from Webster's Third International Dictionary as the pertinent definition:

> A doctrine in law: the terms of a contemporaneous or earlier writing, instrument or document capable of being identified can be made an actual part of another writing, instrument, or document by referring to, identifying, and adopting the former as part of the latter.

The Solicitor in Yang came to the "inescapable" conclusion that the disclosure of the application, as of the filing date of the patented application, had been made an actual part of the patent disclosure. "Any doubt on that score is resolved by the word "hereby" in the patent." In re Yang at 89.

The undersigned respectfully submits that the above-quoted incorporation-by-reference from the papers filed October 6, 2000, leads to the inescapable conclusion

that text of Application Serial No. 08/765,337, was an actual part of the papers filed October 6, 2000.

As further evidence of the acceptability of incorporation-by-reference in U.S. Patent Practice, the Examiner is requested to consider MPEP § 2163.07(b), which states as follows:

> Instead of repeating some information contained in another document, an application may attempt to incorporate the content of another document or part thereof by reference to the document in the text of the specification. **The information incorporated is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed.** Replacing the identified material incorporated by reference with the actual text is not new matter. **See MPEP § 608.01(p)** for Office policy regarding incorporation by reference. (Emphasis added.)

The Examiner is also requested to see MPEP § 608.01(p).

Finally, the Examiner is requested to see the attached "Claiming Benefit of a Prior-Filed Application Under 35 U.S.C. §§ 119(e), 120, 121, and 365(c)" issued by Stephen G. Kunin, Deputy Commissioner for Patent Examination Policy, on February 24, 2003, wherein in Part VII (pages 8-9), the Patent Office states that an amendment to add an incorporation-by-reference of a prior application after the filing date will be considered as an attempt to add new matter. The applicants submit that these comments implicitly allow for incorporation-by-reference of prior applications in the original application papers, as was the case with the present application.

Withdrawal of the new matter objection is requested.

The Section 103 rejection of claims 10-15 over Curtis (U.S. Patent No. 5,073,627) in view of Yamasaki (EP 0335423) to de Sauvage (Nature 369:533-538) and Souza (U.S. Patent No. 4,999,291), is traversed. Reconsideration and withdrawal of the

rejection are requested in view of the following comments as well as the attached Declaration of Dr. Shiotsu and related article.

Claims 10 to 15 relate to a fusion protein of G-CSF and TPO having an activity of differentiating a pluripotential blood stem cell into a granulocytic cell and a megakaryocytic cell.

The Examiner appears to rely on the following statement of Souza et al. to assert that there was motivation to make the presently claimed invention from the teachings of the cited art: "Polypeptide products of the present invention may be useful, alone or in combination with other hematopoietic factors or drugs in the treatment of hematopoietic disorders". See, column 4, lines 52-55 of Souza and page 3 of Paper No. 12.

Souza's tenuous suggestion that one "may" be able to combine drugs is, at best, an invitation to experiment further with any and all combinations of "hematopoietic factors or drugs" to find a "useful" combination. Such an invitation to further experiment however can not support or establish a prima facie case of obviousness. The Section 103 rejection of claims 10-15 should be withdrawn.

Moreover, Souza et al., does not provide any specific description concerning what type of diseases can be expected to be treated by administration of any type of hematopoietic factor or drug together with G-CSF.

Curtis discloses at col. 1, line 66 to col. 2, line 10, that there are some cases where ligands for receptors of two hematopoietic factors (specifically GM-CSF and IL-3) are able to competitively bind, or where two ligands (i.e., GM-CSF and IL-3) bind a single receptor (see, column 2, lines 8-9 of Curtis). As GM-CSF and IL-3 are taught by Curtis to have overlapping affinity for receptors, there would not have been an expectation that the combination of GM-CSF and IL-3 in a fusion protein would have a

synergistic or even a combined positive effect, as apparently demonstrated in Table A of Curtis. Moreover, Example 8 of Curtis appears to indicate that the activity of the fusion protein of GM-CSF and IL-3 is dependent to some degree on whether the target cell contains receptors for IL-3 but not GM-CSF (i.e., JM-1 cells), or receptors for GM-CSF but not IL-3 (i.e., HL-60 cells), or receptors for both GM-CSF and IL-3 (i.e., KG-1 cells). The activity of a fusion protein of proteins with overlapping activity therefore was unpredictable (see, col. 1, lines 27-28 of Curtis wherein GM-CSF and IL-3 are described as having "considerable overlap in their broad range of biological activities").

The Examiner's reliance on Souza therefore for an alleged motivation to make fusion proteins from any and all hematopoietic factors or drugs, without requiring an undue amount of experimentation, is believed to be contrary to the expectations of one of ordinary skill in the art.

That is, the combination of hematopoietic factors or drugs, even those with such a considerable overlap in a broad range of biological activities, such as GM-CSF and IL-3, may have produced no additional effect or even possibly a competitive decrease in effect. Curtis therefore suggests that the effects of combinations of hematopoietic factors, either as a combination of factors administered together or as a fusion protein, was not obvious.

The secondary art cited by the Examiner does not overcome these teachings of Curtis. One would not conclude from the cited art that co-administration of G-CSF and another hematopoietic factor or drug could be combined, as in the presently claimed invention, to increase platelet and neutrophil production.

As for the Examiner's criticism of the results of Tables 7 and 8 of the present application, further consideration of the following and attached are requested.

The attached Declaration includes additional data which demonstrates the same result as in Table 7 of the specification. Thus, the expression rate of CD61 expressing cells when the fusion protein of G-CSF with TPO is administered is about three-fold at 1.0 ng/ml and about two-fold at 100 ng/ml as compared with the case where G-CSF and TPO are administered together. Accordingly, the applicants and the declarant believe the data of the application is reliable.

In addition, as compared with the case where G-CSF and TPO are administered together (i.e., combination administration), the rate of the expression of Gr-1 cells (granulocytic cells) upon administration of the fusion protein of G-CSF with TPO (i.e, fusion protein administration) is lower at high concentrations [(at 100 ng/ml, 49.2%:41.0% (Table 7), 60.1%:42.8% (additional test result)]. The applicants believe that since TPO also has an activity of differentiation of blood stem cells to granulocytic cells (refer to Table 7 and to the column of single administration of TPO in the additional test result), the rate of expression of Gr-1 cells becomes higher by administration of high concentrations when G-CSF and TPO are administered together and, as a result, there is a tendency that differentiation into CD 61 expression cells is suppressed at high concentration.

However, when the fusion protein of G-CSF with TPO is administered, the rate of Gr-1 expression does not become high even by administration of high concentration and, in addition, differentiation into the CD-61 expression cells is not simultaneously suppressed.

The applicants submit that because the experiments of Test Example 3 involved a large number of mononuclear cells, the results of the two experiments (i.e., one set of results in the specification and one set of results in the attached Declaration) should

sufficiently demonstrate whether the mononuclear cells tend to differentiate into megakaryocytes, alternatively whether they tend to differentiate into granulocytes, when a combination of G-CSF and TPO or a fusion protein of G-CSF and TPO is administered.

The results in Table 7 and the attached Declaration data show that both CD61 cells and Gr-1 cells are expressed with an acceptable ratio by the fusion protein administration with higher administration concentrations, in comparison with the combination administration. That is, since TPO *per se* has activity to differentiate blood stem cells (corresponding to mouse mononuclear cells in Test Example 3) into granulocytes (corresponding to Gr-1 cells in Test Example 3), the ratio of Gr-1 expressing cells becomes higher as the administration concentration of the combination administration becomes higher. Thus, as shown in Table 7, the ratio of CD61 expressing cells which are megakaryocytes becomes small. These results can be expected from the knowledge in the art.

On the other hand, the ratio of Gr-1 expressed cells is not increased and the differentiation into CD61 expressed cells is not inhibited in the fusion protein administration, in comparison with the combination administration. Accordingly, the results show that the fusion protein administration can increase neutrophils and platelets simultaneously.

The difference of effects *in vitro* between the combination administration and the fusion protein administration is remarkable in higher administration concentrations as discussed above. Accordingly, even if an *in vitro* difference is not shown in the experimental results shown in Table 8, it cannot be concluded that there is no difference between the combination administration and the fusion protein administration.

These results suggest therefore that when G-CSF and TPO are administered together, but not as a fusion protein, it may be possible to promote the differentiation into granulocytic cells and to increase the leukocyte numbers, however differentiation into megakaryocytic cells is not well promoted and sufficient amounts of platelets are not produced. Moreover, the applicants submit that when the fusion protein of G-CSF and TPO is administered, nearly the same amount of Gr-1 expressing cells are obtained as in the case of single administration of G-CSF. Further, as compared with the administration of G-CSF and TPO together, CD61 expressing cells are produced at a level of two- to three-fold. This is believed to provide a significant and unexpected advantage. The presently claimed invention therefore increases leukocyte and platelet numbers.

Table 8 of the present applications shows that the fusion protein of G-CSF with TPO is able to increase both platelets and leukocytes *in vivo*.

Although it may be true in Table 8 that, as compared with the case of mice receiving a single administration of TPO, platelet numbers of mice administered with the fusion protein are reduced (0.2 ml of a 10 μg/m1 solution of TPO or fusion protein was administered per 20 g body weight of mouse in the *in vivo* test of Test Example 4). The total blood volume of a mouse of 20 g body weight is about 1.5 to 2.0 ml, such that the concentration of TPO or the fusion protein in blood however upon administration is 1.0 to 1.3 μg/ml, which is 10-fold greater that the largest concentration tested in the in vitro test of Table 7. The results of Tables 7 and 8 therefore may not be directly comparable, as suggested by the Examiner at page 4 of Paper No. 12.

That is, the applicants believe that it cannot be concluded from the data of Table 8 that there is no significant difference in activities in vivo between "a combination of G-

CSF and TPO" and "a fusion protein of G-CSF with TPO". When administering G-CSF together with TPO to mice, one of ordinary skill in the art will appreciate that increasing the platelet numbers by increasing the dose of TPO alone at high concentrations causes thrombocytosis and fibrosis [see the attached reference: Blood, 87, 5006-5015 (1996), page 5006, left column, last line to page 5007, left column, line 8]. An increase of dose of TPO does not necessarily result therefore in the treatment of diseases but rather causes the risk of causing a further hematopoietic disease.

The data shown in Table 7 reliably demonstrates that, as compared with the combined use of G-CSF and TPO, the fusion protein of G-CSF with TPO is able to appropriately increase granulocytic and megakaryocytic cells. The claimed invention provides this unexpected benefit.

The Examiner has asserted that these effects may be merely due to an alleged larger size of the fusion protein as the Examiner asserts that larger proteins can be more stable, and take loner to degrade. See, page 4 of Paper No. 12.

As described at page 53, lines 16 to 17 in the specification, however the TPO and the fusion protein of TPO with G-CSF used in Table 7 of the specification are the proteins prepared in Example 3. Therefore, TPO is a protein comprising 332 amino acids (Table 3 of the specification) prepared in Example 2-2 while the fusion protein of G-CSF with TPO is a protein encoded by DNA prepared in Example 1-3, i.e., a protein of 345 amino acids (SEQ ID NO:6).

Therefore, as compared with TPO, the molecular weight of the fusion protein of G-CSF with TPO is greater than that of TPO by only 13 amino acids. The Examiner's conclusion therefore is not believed to be supported by the facts.

As noted above, the comments of the cited art with regard to combining hematopoietic factors or drugs, even taken with Curtis and the other cited art, was not sufficient to motivate one of ordinary skill in the art to make the presently claimed invention with any reasonable likelihood of success. This is even further demonstrated by the applicants experimental data.

Specifically, when G-CSF and TPO are administered together, the rate of cells differentiating to granulocytic cells is high as compared with a single administration of TPO but the rate of cells differentiating to megakaryocytic cells is the same or even less and, especially in the case of administration of high concentration, the rate of cells differentiating to megakaryocytic cells is low. However, when the fusion protein of G-CSF with TPO is administered, the rate of cells differentiating to granulocytic cells is higher than a single administration of TPO and the rate of cells differentiating to megakaryocytic cells is the same or even more. Such a result is not suggested from the result that the fusion protein of IL-3 with G-CSF promotes the differentiation of granulocytic cells or that GM-CSF may be usefully administered with other hematopoietic factors or drugs.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

NIXON & VANDERHYE P.C.

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